

REMARKS

The Office Action

Claims 1-3, 5-11, and 21-22 are pending in this application and were examined. Claims 12-13 were withdrawn from consideration as being drawn to non-elected inventions.

The Examiner's attention is respectfully drawn to claim 21, still under consideration. It appears that this claim was inadvertently assumed to be withdrawn. Applicants point out that claim 22 is drawn to a range of average liposome sizes that is more narrow but falls mostly within the range of claim 21. Accordingly, Applicants assume that all rejections applied against claim 22 were intended to apply against claim 21 and have replied accordingly. Applicants hereby request that claim 21 be rejoined for further examination.

Claims 1-3 and 8 stand rejected under 35 U.S.C. § 102 as anticipated by Hafez et al. (*Biophysical Journal*, 79: 1438-1446, 2000; "Hafez"). Claims 9-11 and 22 stand rejected under 35 U.S.C. § 103(a) as obvious over Hafez. Claims 1-3, 5-11, and 22 stand rejected under 35 U.S.C. § 103(a) as obvious over Deshmukh et al. (U.S. Patent 6,258,792; "Deshmukh") alone or, in the alternative, over Hafez in view of Deshmukh.

Status of Claims

This paper amends claims 1, 3, 5-9, and 11, and adds claims 23-60. Claims 1-3, 5-11, and 21-60 are currently under examination.

Support for Amendments

The amendment to the specification is made to correct an obvious error in translation from the priority document.

Support for the amendment to claim 1 is found in claims 2 and 7.

Support for the amendment to claim 3 is found in claim 7.

Claim 7 is amended to correct obvious typographical errors.

Support for newly added claims 23-52 is found throughout the specification and, for example, at page 5, fifth paragraph through page 7, and examples 1-8 on pages 15-23.

Information Disclosure Statements

Applicants respectfully request that the Examiner return to Applicants an initialed copy of the PTO-1449 form that was submitted on October 8, 2002.

Rejections Under 35 U.S.C. § 102

Claims 1-3, 5-11, and 21-22 stand rejected under 35 U.S.C. § 102 as anticipated by Hafez. Insofar as this rejection applies to claims 1-2, 8-11, and 21-22, the rejection is overcome by the present amendment which requires that the amphoteric liposomes further contain a neutral lipid. Support for this amendment is found in pending claim 7 which the Examiner did not reject as anticipated by Hafez. Therefore, amended claim 1, and all claims that depend from claim 1, are no longer anticipated by Hafez and withdrawal of this rejection is respectfully requested.

As this rejection is applied to claims 3, 4, and 6, Applicants respectfully traverse. The liposomes of claim 3 require the presence of at least one amphipatic lipid having both a positive charge and a negative charge. The liposomes of Hafez contain mixtures of positively charged lipids and negatively charged lipids (see, Abstract). Nowhere does Hafez teach the use of a single lipid that carries both a positive and a negative charge. Applicants point out that claim 3 has been further amended to require the presence of a neutral lipid—another element not present in the Hafez liposomes. Accordingly, claims 3, 4, and 6 are not anticipated by Hafez and withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. § 103

Rejection over Hafez

Claims 9-11 and 21-22 stand rejected under 35 U.S.C. § 103(a) as obvious over Hafez. Applicants again note that claim 1 is hereby amended to require that the liposomes contain a cationic lipid, an anionic lipid, and a neutral lipid. These limitations are necessarily incorporated into the currently rejected claims. Nothing in Hafez teaches or suggests liposomes that contain each of these lipid types. Accordingly, this rejection should be withdrawn and such action is respectfully requested.

Rejection over Deshmukh

Claims 1-3, 5-11, and 21-22 stand rejected under 35 U.S.C. § 103(a) as obvious over Deshmukh. Specifically, the Examiner asserts that Deshmukh teaches the use of cationic cholesterol derivatives with, *inter alia*, cholesterol hemisuccinate in the preparation of liposomes. The Examiner concludes that it is obvious to a person of ordinary skill in the art to combine the cationic cholesterol derivatives of Deshmukh with the anionic cholesterol hemisuccinate. Applicants respectfully traverse the Examiner's reading of Deshmukh.

Deshmukh teaches liposomes containing the cationic cholesterol hemisuccinate choline ester (ChOSC); not liposomes containing the anionic cholesterol hemisuccinate (CHEMS). There is an omission in the specification of Deshmukh that leads to confusion. In characterizing known cationic lipids, Deshmukh states:

Among the numerous cationic amphiphiles which have been referred to as useful for transfecting nucleic acids into cells are cationic derivatives of cholesterol. For example... cholesterol hemisuccinate choline ester (ChOSC) contains a choline moiety connected to the 3'-hydroxyl group via a succinyl spacer arm.

Deshmukh at column 2, lines 17-25 (emphasis added).

Later, in a portion of the specification upon which the Examiner relies, Deshmunk incorrectly states:

Suitable cationic lipid species which may be combined with the compounds of the invention include, but are not limited to... cholesterol hemisuccinate ester (ChOSC).

Deshmukh at column 6, lines 50-66 (emphasis added).

Deshmukh incorrectly uses the abbreviation "ChOSC" for different molecules from one passage to another. Clearly the latter usage of ChOSC in Deshmukh (at col. 6) is incorrect. Deshmukh is describing known cationic lipids that may be combined with the cationic lipids of his invention to form liposomes. Cholesterol hemisuccinate, having the art-recognized

abbreviation of CHEMS, is an anionic lipid and its use here is inconsistent with the rest of the teachings. It is obvious that Deshmukh meant to refer to the cationic cholesterol hemisuccinate choline ester, as he did earlier in the specification. This interpretation is consistent with the ChOSC abbreviation and the context of the teachings. Accordingly, Deshmukh does not specifically suggest constructing liposomes using the anionic cholesterol hemisuccinate (CHEMS) in combination with cationic lipids, as asserted by the Examiner.

Under either interpretation of Deshmukh, however, Applicants traverse this rejection with the present amendments. Specifically, claim 1 is amended to require that the isoelectric point of the claimed liposomes is between 4 and 7. Deshmukh, by contrast, specifically requires cationic liposomes. See, for example, column 7, lines. 33-35 and lines 46-51. Claims 1-2, 7-11, and 21-22, as currently amended, are not obvious in view of Deshmukh.

Claims 3, 5, and 6 are not rendered obvious by Deshmukh. Claim 3 (from which claims 5 and 6 depend) requires that the amphoteric liposomes contain a lipid that carries both a positive and a negative charge. Nowhere does Deshmukh teach or suggest using these doubly-charged lipids in the preparation of liposomes.

Applicants respectfully submit that this rejection is traversed by the present claim amendments and clarification of the Deshmukh specification. This rejection may be withdrawn.

Rejection over Hafez in view of Deshmukh

Claims 5-11 and 21-22 stand rejected under 35 U.S.C. § 103(a) as obvious over Hafez in view of Deshmukh. Specifically, the Examiner characterizes Hafez as disclosing liposomes containing cholesteryl hemisuccinate (CHEMS; an anionic lipid) and DODAC (a cationic lipid), and having a pH_f of 4 – 6.7. The Examiner notes that Hafez lacks a teaching to include another lipid and an active agent. The Examiner asserts that it would have been obvious to combine the teachings of Deshmukh—to include a neutral lipid and an active agent such as DNA, RNA, or proteins—with those of Hafez to arrive at the presently claimed invention. Applicants respectfully traverse.

In order to make a *prima facie* case of obviousness, the Examiner must demonstrate that the prior art provides a motivation to combine the teachings of the selected references. It is well established that prior art references are not properly combined, and fail to establish a *prima facie* case of obviousness, if their combination or modification renders the device inoperable for its intended purpose. *In re Gordon*, 733 F.2d 900, 221 U.S.P.Q. 1125 (Fed. Cir. 1984) (not obvious to turn the prior art device upside down because it would render the device inoperable); *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 20 U.S.P.Q.2d 1746 (Fed. Cir. 1991).

The teachings of Hafez and Deshmukh cannot be properly combined because these references have different requirements that are mutually exclusive. Hafez teaches the creation of liposomes having a pH_f of 4 – 6.7 (i.e., that are anionic at physiological pH). Deshmukh requires cationic liposomes (col. 7, lines. 33-35 and col. 7, lines. 46-51). It is impossible for a liposome to be simultaneously anionic (satisfying Hafez) and cationic (satisfying Deshmukh) at physiological pH. The requirements of these two references, therefore, renders the combination of references improper. Such a combination of references cannot be used to support a *prima facie* case of obviousness.


Accordingly, in view of the present claim amendments and foregoing arguments, Applicants submit that the combination of Hafez and Deshmukh does not render the instant invention obvious. This rejection should be withdrawn and such action is respectfully requested.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested. If the Examiner should have any questions concerning this communication or feels that an interview would be helpful to expedite allowance of this case, the Examiner is requested to call Applicants' undersigned attorney.

Respectfully submitted,

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